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EXAMINER	
VAKILI, ZOHREH	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/538,277	SOTO PEREDO, CLAUDIA ANGELICA	
	Examiner	Art Unit	
	ZOHREH VAKILI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10-16 and 27-30* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 27-30 are presented for examination.

Applicant's Amendment filed December 18, 2007 has been received and entered into the present application. Claims 27-30 are pending and are herein examined on the merits.

Applicant's arguments, filed December 18, 2007 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Maintained Claim Rejections - 35 USC § 103

The rejection of claims 27-30 under 35 U.S.C. 103(a) as being unpatentable over Bibbs et al. (U.S. Pub. No. 2004/0006128), in view of Soto et al. (Comp. Biochem. Physiol. Vol. 119C, No. 2, p. 125-129, 1998, Cited on IDS), and further in view of Coote et al. (U.S. Pub. No. 2004/0167034 A1) has been maintained for the reasons stated in the prior Office Action June 19, 2007 and further in view of the following remarks.

Bibbs et al. teach methods of treating a mammal with high blood-glucose, or high blood-cholesterol and pharmaceutical compositions comprising the same are disclosed (see abstract). Diabetes mellitus is a chronic condition characterized by the inability to regulate blood glucose levels. Diabetes mellitus is a metabolic disorder of the human body primarily involving an

inability of the body to properly store and utilize sugar and other chemical compounds in the metabolism of the body. It is characterized by an elevation in the concentration of sugar in the blood and also by the appearance of sugar in the urine (see page 1, paragraph 0005). Diabetes mellitus is classified into two types, namely, Type I and Type II. In Type I diabetes, the beta cells in the pancreas, probably through an auto-immune reaction, cease production and secretion of insulin into the bloodstream. Insulin is a hormone that is normally secreted into the bloodstream by beta cells within the pancreas. Insulin enables the body to properly utilize and store (as fat) the sugars that enter the bloodstream as part of the digestive process (see page 1, paragraph 0006). In Type I and Type II diabetes, the pancreas continues to produce insulin but some or all of the insulin may fail to bind to the body's cell receptors and/or internalization of insulin in the cells is reduced. In such cases, there may be a sufficient level of insulin in the blood, but the ability of the cells to uptake glucose is reduced (see page 1, paragraph 0008). Bibbs et al. disclose a method of treating a mammal with high blood glucose (see page 1, paragraph 0009). The administered composition comprises less than 40% of other naturally occurring bioflavanoids, while in other embodiments, the composition comprises less than 35% of other naturally occurring bioflavanoids. In yet other embodiments, the composition comprises less than 30%, less than 25%, less than 20%, less than 15%, or less than 10% of other naturally occurring bioflavanoids. In certain embodiments, the composition comprises less than 5% of other naturally occurring bioflavanoids (see page 1, paragraph 0015). The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes (see page 4, paragraph 60). For oral administration, the compounds can be formulated readily by

combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more compound of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl cellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate (see page 4, paragraph 63). Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses (see page 4, paragraph 64). Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as

fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration (see page 4, paragraph 65). For buccal administration, the compositions may take the form of tablets or lozenges (see page 4, paragraph 0066).

Soto et al. teach silymarin a flavonoid extracted from the milk thistle Silybum marianum. This compound has shown protective effects against the oxidative peroxidation of cells. Silymarin functioned as a free radical scavenger, increasing available GSH and preventing membrane alterations. The evidence seems to indicate that diabetes mellitus and its sequels are conditions in which free radicals are involved both in human beings and in experimental models. Alloxan administration causes severe necrosis of pancreatic beta cells. Given these hypotheses, the above model was considered adequate for the study of a pathology in which free radicals might have a central role, such as diabetes mellitus. The aim of this study was to evaluate the effect of the antioxidant silymarin on the alloxan-induced diabetes mellitus, since its potential protective effects have been previously addressed in other models of cell damage induced by drugs (see page 125, introduction). The main finding of this study was that silymarin prevented a rise in both plasma glucose and pancreatic lipid peroxidation induced by alloxan in rats. This result suggests a protective effect of silymarin against alloxan action. These observations of the effect of silymarin in the area of hepatocyte protection may contribute to explaining why this compound has a protective effect on pancreatic lipid peroxidation with the recovery of the beta cell function. This, in turn, may contribute to the regulation of plasma glucose. It has been suggested that thiol groups are important in the intracellular and membranal redox state of the secretory function of beta pancreatic cells. Silymarin induced an increase in pancreatic glutathione content which may enhance the GSH/GSSG

ratio and therefore improve plasma glucose regulation. This study suggests that the induction of diabetes mellitus by alloxan in rats may be prevented by silymarin administration. This drug had a favorable effect on the pancreatic damage produced by the production of free radicals. This is the case in the experimental model of diabetes mellitus induced by alloxan and is probably the case in human diabetes mellitus type I (see page 128 & 129, Discussion).

Coote et al. teach of a process of preparing an emulsion, a composition comprising the emulsion to be administered to human or animal (see page 1, paragraph 0001). Flavonoids phytosterols, carotenoids, and other phytochemicals are classes of compounds isolated from plants with recognized pharmacological properties. Flavonoids demonstrate free radical scavenging properties (see page 1, paragraph 0003). Coote et al. further disclose liquid dosage forms for oral administration may include pharmaceutically acceptable (or veterinarilly acceptable where the dosage form is intended for animals) in the case of acceptable emulsions, syrups, solutions, suspensions, and elixirs containing inert diluents commonly used in the art, such as water (see page 5, paragraph 0060). A preferred thickening agent is carbopol or equivalent thickening agents (see page 5, paragraph 0061). Solid dosage forms for oral administration may include capsules. In such forms, the emulsion may be admixed with at least one inert diluent such as silicas, dicalcium phosphate, sugars, talcs. In the case of capsules, the dosage forms may also comprise buffering agents. The capsules can additionally be prepared with enteric coatings (see page 5, paragraph 0062). The processes of the present invention are applicable to synthetic drugs, plant and animal compounds plant flavonoids which comprises various subclasses such as flavans, flavanones, flavones, anthocyanins etc. Flavonoids may be monomeric, dimeric, oligomeric and may also exist in free or glycosidic forms phytoestrogens. Flavanolignans from silymarin, and animal compounds

such as glucosamine and chondroitin sulphate and hydrophobic synthetic drugs, natural compounds from plants and animals such as carotenoids, lycopene, lutein, tocopherols, phytosterols and waxes such as policosanols (see page 5, paragraph 0067). 50 g water, 300 mg glucosamine hydrochloride and 2 g chondroitin sulphate were mixed. To this was added 2 g excipient (thickening agent, eg. Carbopol) (see page 7, paragraph 0095). Formulation for 100 g of gel: Complex preparation (as in Examples 1-10). 50 g Triethanolamine 1 g Carboxyvinyl polymer (carbopol 934^{R}) 1.5 g Perfume 0.1 g Sodium hydroxybenzoate 0.2 g Isopropylmyristate 1.0 g d-limonene 0.5 g Distilled water qs to 100 g (see page 8, paragraph 0096). Hepatic formulation consisted of the following: 16.67 kg silymarin (70:1), 6.67 kg Bupleurum falcatum (5:1) and 6.67 kg Schisandra chinensis (16:1). This mixture was then added to 45.67 kg of phytosterol base and tabletised (see page 9, paragraph 0143).

One of ordinary skill in the art would combine the teachings of Bibbs et al. in view of Soto et al., and further in view of Coote et al. Bibbs et al. disclose a composition for lowering blood glucose level. The administered composition comprises less than 10% flavanoids. The pharmaceutical composition for oral administration is formulated as tablets, pills, and suspension and for suitable coating carbopol gel is used. The composition is to treat diabetes mellitus. In Type I diabetes, the beta cells in the pancreas cease production and secretion of insulin into the bloodstream. Soto et al. uses silymarin a flavonoid that functions as a free radical scavenger to a patient with diabetes mellitus induced with alloxan that causes severe necrosis of pancreatic beta cells. Silymarin has shown protective effects of cell damage induced by drugs. Coote et al. disclose pharmaceutical formulations for oral administration such as oral suspension where the flavonoid

silymarin is used in different concentrations and in one composition carbopol is used in 2 grams and in another 1.5 grams.

It would have been obvious to a person skilled in the art to employ the teachings of Bibbs et al. in view of Soto et al., and further in view of Coote et al. considering that such references teach all the components of the claimed invention in a pharmaceutical formulation. The optimal dosage amounts would have been obvious to the skilled artisan. The determination of a dosage of the active ingredient are well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug while minimizing adverse or unwanted side effects or even undesirable stability issues. Thus, one of ordinary skill in the art would have been motivated to combine the teachings of the above references and as combined teach the invention as claimed.

One skilled in the art would have been motivated to employ the teachings of Bibbs et al. in view of Soto et al., and further in view of Coote et al. The above references make clear that the claimed components have been previously used in a biological pharmaceutical composition. As combined, the references would have resulted in the claimed invention. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, prima facie obvious over the cited arts.

Response to Arguments

Applicant has added new claims to indicate a method of recovering endocrine pancreatic function administering to a patient a composition comprising Silymarin and Carbopol, capable of regenerating damaged pancreatic cells.

Applicant argues that although Bibbs et al. teaches using a bioflavanoid to lower blood glucose in an organism along with carbopol, further argues although silymarin is a bioflavanoid, its choice as a regenerator of endocrine pancreatic function is not obvious due to the great variety of existing bioflavanoids found in nature.

Examiner does not agree it is well within the skilled artisan to distinguish which bioflavanoid can be used to lower blood glucose and any bioflavanoid that has the ability to lower the blood glucose it is inherent of that compound to have characteristics such as to regenerator endocrine pancreatic function. It is also disclosed by Soto et al. that silymarin, an antioxidant, is used to lower blood glucose and it does so by preventing cell damage of pancreatic tissue and further highlights that silymarin has a protective effect in diabetes mellitus. As discussed above there is no need for Soto et al. to disclose that silymarin has regenerative effect. Silymarin is used to prevent damage to the pancreatic tissue, therefore the regenerative activity of this compound is an inherent characteristic and obvious of this compound.

Applicant argues that carbopol is not taught by any of the above mentioned references. Examiner draws Applicant's attention to Bibbs et al. and Coote et al. both references teach a flavanoids in combination with carbopol. Carbopol is a polymer that is used in formulations as stabilizer, binder, and thickener. Carbopol is a known excipient that is regularly being used in dentifrices, pharmaceutical formulations, etc. as it is being used here in the instant claimed invention as a binder or stabilizer of the formulation. It's functionality is only to bind the formulation. Patel (US Patent No. 4844883) teaches binders and thickeners in its composition that are generally used in concentrations of about 0.5% to about 2% by weight. Exemplary thickening agents include

polyvinylpyrrolidone and cross-linked acrylic acid polymers available under the designation Carbopol (see col. 8, lines 44-54).

For these reasons, and those already made of record at pages 3-10 of the previous Office Action dated June 19, 2007, of which such reasons are incorporated herein by reference, rejection of claims 27-30 remain proper and is **maintained.**

Applicant's amendments and remarks have been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

Conclusion

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner 1614 May 20, 2008

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614